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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,925	07/11/2001	Avi Ashkenazi	10466/86	1358
35489	7590	01/14/2004	EXAMINER	
HELLER EHRMAN WHITE & MCAULIFFE LLP 275 MIDDLEFIELD ROAD MENLO PARK, CO 94025-3506			HAMUD, FOZIA M	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/903,925	ASHKENAZI ET AL.
	Examiner	Art Unit
	Fozia M Hamud	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 22 September 2003.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 45-49 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 45-49 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All
 - b) Some *
 - c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 13) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
 - a) The translation of the foreign language provisional application has been received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) Interview Summary (PTO-413) Paper No(s) _____
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____

DETAILED ACTION

Request for RCE:

1a. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 22 September 2003 has been entered. Claims 39-43 have been canceled and new claims 45-49 have been entered in the amendment filed on 23 September 2003.

Status of Claims:

1b. Claims 1-44 have been cancelled. Claims 45-49 are pending and under consideration.

1c. Receipt of Applicant's declaration under 37 C.F.R §1.132, filed by Dr. Avi Ashkenazi 22 September 2003 is also acknowledged.

2. Priority:

Applicants submit that the results of the gene amplification assay disclosed in parent applications PCT/US99/30095, filed 16 December 1999 (WO 00/37640), and 60/113,296 filed on 22 December 1998, provide a specific and substantial asserted utility for the antibodies claimed in the present application. Therefore, Applicants contend that the present application is entitled to the filing date of 22 December 1998. This argument is not found persuasive. The claims of the instant invention are drawn to a method of diagnosing lung or colon cancer using an antibody that binds to the

polypeptide of SEQ ID NO:263. However, said subject matter is not supported by the disclosure in the international application PCT/US99/30095, filed 16 December 1999 or in the provisional application No:60/113,296 filed on 22 December 1998, since these prior applications do not provide a specific and substantial asserted utility or a well established utility for the claimed invention. As was previously stated, the gene amplification assay described in the parent applications provide a specific and substantial asserted utility for the polynucleotide of SEQ ID NO:262, because the assay shows approximately 2-9 fold amplification of DNA sequences in lung and colon tumors compared to normal controls. However, the increased copy number of PRO343 DNA in lung and colon tumors, does not provide a readily apparent use for the polypeptide or the antibodies against the polypeptide, because the assay does not show that the polypeptide is also amplified in these tumors.

Accordingly, the subject matter defined in claims 45-49 is afforded an effective filing date of 07/11/2001 which is the filing date of the current application.

Claim Rejections under 35 U.S.C. §101/112:

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3a. Claims 45-49 are rejected under 35 U.S.C. §101, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Instant claims 45-49 are drawn to a method for diagnosing lung or colon cancer by contacting a lung or colon tissue with antibodies that bind to the polypeptide of SEQ ID NO:263, in which the presence of said polypeptide is an indication that the subject has lung or colon cancer. However, instant specification does demonstrate that the polypeptide of SEQ ID NO:263 is expressed or amplified in lung or colon tumors, compared to normal controls.

Applicants argue that the Examiner has not established that it is more likely than not that one of ordinary skill in the art would doubt the truth of their statement of utility. Applicants also argue the fact that Pennica et al disclose a specific class of closely related molecules have no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general that such correlation does not exist. Applicants contend that the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. Finally, Applicants argue that even if the gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

These arguments have been fully considered, but are not deemed persuasive. Firstly, the instant specification has not shown that the polypeptide of SEQ ID NO:263 is expressed at all or is overly expressed in lung or colon tumor tissues. Thus, there is no correlation established between the polypeptide of SEQ ID NO:263 and lung or colon cancer or any other disease. Accordingly, instant specification does not provide a

specific or substantial utility for the polypeptide of SEQ ID NO:263, the antibodies binding to said polypeptide or a method of using said antibodies. Secondly, contrary to Applicants' argument, the art does not recognize that protein levels are increased when gene amplification occurs. Although the Pennica et al reference only represents one class of proteins, and shows a lack of correlation between this class of protein and gene amplification, however, other researchers have also demonstrated a lack of correlation between gene amplification and protein expression. For example, Haynes et al (1998, Electrophoresis, Vol. 19, pages 1862-1871), studied more than 80 proteins which were relatively homogenous in half-life and expression, and found no strong correlation between protein and transcript level. Haynes et al showed that for some genes, equivalent mRNA levels translated into protein abundances, which varied more than 50-fold. Haynes et al concluded that the protein cannot be accurately predicted from the level of the corresponding mRNA transcript, (see page 1863, second paragraph and Figure 1). See also, Konopka et al (Proc. Natl. Acad. Sci, 1986, vol.83, pages 4049-4052), who state that "protein expression is not related to amplification of the ab1 gene but to variation in the level of a bcr-ab1 mRNA produced from a single ph1 template", see abstract. Therefore, the art indicates that it is not the norm that gene amplification or increased transcription results in increased protein level. Accordingly, showing that the DNA encoding the polypeptide of SEQ ID NO:263 is present in increased copy number in a lung and colon tumor is not sufficient to establish any utility for the protein encoded thereby or the antibody that binds to said protein. Finally, Applicants' last argument is an invitation for more experimentation. Since the instant specification

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establishes no correlation between the polypeptide of SEQ ID NO:263 and lung or colon cancer, the clinician would have no reason to measure the levels of said polypeptide in an attempt to diagnose colon or lung cancer. Furthermore, the instantly claimed invention is drawn to a method of diagnosing lung or colon cancer by using antibodies that bind to the polypeptide of SEQ ID NO:263, in which the expression of said polypeptide is an indicative of colon or lung cancer. Therefore, if the gene amplification does not correlate with the over-expression of the polypeptide of SEQ ID NO:263 in lung and colon tumor tissues, one of ordinary skill in the art would not be able to predict whether the lack of said expression equates to the absence of cancer in the subject.

Therefore, the method for diagnosing lung or colon cancer by contacting a lung or colon tissue with antibodies that bind to the polypeptide of SEQ ID NO:263, claimed in instant claims 45-49 is not supported by either a specific and substantial asserted utility or a well established utility, because Applicants have not shown that the polypeptide of SEQ ID NO:263 is increased in lung or colon tumors compared to normal controls.

3b. Claims 45-49 are also rejected under 35 U.S.C. 112, first paragraph.

Specifically, the increased copy number of PRO343 DNA in lung and colon tumors, does not provide a readily apparent use for the polypeptide or the antibodies against the polypeptide, because there is no information regarding the level of expression, an activity, or a role in cancer for the PRO343 polypeptide or antibodies which bind to said polypeptide, for the antibodies to be used diagnostically.

37 CFR 1.132 Declaration:

4. The declaration under 37 C.F.R §1.132, filed on 22 September 2003 is being considered to evaluate whether claims 45-49 are supported by either a specific and substantial asserted utility or a well established utility.

The Declaration submitted by Dr. Ashkenazi has been fully considered, however, this declaration fails to provide a specific and substantial asserted utility or a well established utility for claims 45-49 of the instant application. Dr. Ashkenazi describes the gene amplification technique in which chromosomes undergo changes to contain multiple copies of certain genes that normally exist as a single copy and attests to the importance of this in the pathophysiology of cancer. Dr. Ashkenazi submits that even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Dr. Ashkenazi also states that if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel gene monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy.

The importance of gene amplification technique in the pathophysiology of cancer is not disputed. However, if the gene amplification does not result in over-expression of the gene product, the gene products would not be useful in diagnostic or treatment manner. Dr. Ashkenazi is correct in that parallel gene monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy, however, instant specification has not

under taken said monitoring. The Examiner does not doubt that after further characterization showing that the gene amplification of the polynucleotide of SEQ ID NO:262 in colon or lung tumors, results in either the over-expression of the polypeptide of SEQ ID NO:263, or does not lead to the expression of said polypeptide at all, in these tissues, the polypeptide of SEQ ID NO:263 and antibodies that bind would be useful in cancer diagnosis and treatment. However, further characterization is part of the act of invention and until it has been undertaken, the claimed invention is incomplete. Accordingly, doing further research to determine the level of expression of the polypeptide of SEQ ID NO:263, does not afford said polypeptide or antibodies that bind it, a patentable utility.

Claim rejections-35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 145-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "specifically" recited in claim 45 is a relative term which renders the claim indefinite. The term "specifically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Appropriate correction is required.

Claims 46-49 are also rejected 35 USC § 112, second , because they depend from claim 45.

Conclusion:

6. No claim is allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M Hamud whose telephone number is (703) 308-8891. The examiner can normally be reached on Monday, Wednesday-Thursday, 6:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit 1647
09January 2004

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